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Nutrition issues in Codex: health claims, nutrient reference values and WTO agreements: a conference report

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Abstract: BACKGROUND: Codex documents may be used as educational and consensus materials for member governments. Also, the WTO SPS Agreement recognizes Codex as the presumptive international authority on food issues. Nutrient bioavailability is a critical factor in determining the ability of nutrients to provide beneficial effects. Bioavailability also influences the quantitative dietary requirements that are the basis of nutrient intake recommendations and NRVs. **HEALTH CLAIMS:** Codex, EFSA and some national regulatory authorities have established guidelines or regulations that will permit several types of health claims. The scientific basis for claims has been established by the US FDA and EFSA, but not yet by Codex. Evidence-based nutrition differs from evidence-based medicine, but the differences are only recently gaining recognition. Health claims on foods may provide useful information to consumers, but many will interpret the information to mean that they can rely upon the food or nutrient to eliminate a disease risk. **NUTRIENT REFERENCE VALUES:** NRVs are designed to provide a quantitative basis for comparing the nutritive values of foods, helping to illustrate how specific foods fit into the overall diet. The INL-98 and the mean of adult male and female values provide NRVs that are sufficient when used as targets for individual intakes by most adults. **WORLD TRADE ORGANIZATION AGREEMENTS:** WTO recognizes Codex as the primary international authority on food issues. Current regulatory schemes based on recommended dietary allowances are trade restrictive. A substantial number of decisions by the EFSA could lead to violation of WTO agreements.

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Abstract

Background Codex documents may be used as educational and consensus materials for member governments. Also, the WTO SPS Agreement recognizes Codex as the presumptive international authority on food issues. Nutrient bioavailability is a critical factor in determining the ability of nutrients to provide beneficial effects. Bioavailability also influences the quantitative dietary requirements that are the basis of nutrient intake recommendations and NRVs.

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that will permit several types of health claims. The scientific basis for claims has been established by the US FDA and EFSA, but not yet by Codex. Evidence-based nutrition differs from evidence-based medicine, but the differences are only recently gaining recognition. Health claims on foods may provide useful information to consumers, but many will interpret the information to mean that they can rely upon the food or nutrient to eliminate a disease risk.

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This document is a Conference Report and not a Consensus Statement; therefore, some authors may not agree with all statements included. Also, some speakers at the conference did not participate in the manuscript development and are not listed as authors.

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dietary allowances are trade restrictive. A substantial number of decisions by the EFSA could lead to violation of WTO agreements.

Keywords Codex Alimentarius · Bioavailability · Health claims · Nutrient reference values · World Trade Organization · WTO agreements

Introduction

A previous workshop [1] had reviewed the development of the Codex Alimentarius (Codex) and its central role in protecting the health of consumers and ensuring fair practices in international food trade. This workshop further reviewed how Codex promotes harmonization and consensus by promoting the coordination of Food Standards established by governments and non-governmental organizations. Thus, although it has no statutory authority, it is the guardian of the culture and of the responsible and objective application of the best available science to risk analysis and other issues relating to food. Codex documents have important roles as templates for national regulations, or as the basis for international trade agreements, and they have a distinctive authority and credibility that is derived from their painstaking development of a consensus in a multistep procedure that may take many years. Nevertheless, although this process may delay the final adoption of the document, it provides a basis for subsequent cooperation after its implementation. Codex standards are applied in conjunction with the various agreements—sanitary and phytosanitary (SPS) agreement and technical barriers to trade (TBT) agreement—adopted as part of the rules of the World Trade Organisation (WTO). The SPS agreement in particular requires the use of risk assessment as a component of the overall risk analysis. The risk analysis itself is intended to be congruent with the WTO agreements, but certain elements of risk management and communication may entail some contextualization according to diverse cultures and socio-economic situations. The latter may lead to discrepancies in practice and policy leading to disputes which need WTO arbitration. The fundamental risk assessment and its quality, whether it is performed within Codex or elsewhere, is crucial to this process. Thus, in the widest context, Codex documents have been helpful to member governments, industry and consumers. An important outcome is that the documents have been used in the past 20 years to promote coordination of approaches to setting dietary and nutrient reference values, standardization of nutrient and health claims and a systematic approach to nutrient risk assessment and the setting of upper levels of intake or exposure.

Nutritional science, causal inference and health claims

These developments both individually, and overall, demonstrated a need for an appropriate focus of developments in nutritional research, and in particular, the expected introduction of health claims was anticipated by what could be seen as a renaissance of food science. The European Union and International Life Sciences Institute—Europe (ILSI-Europe) coordinated Concerted Action, “Functional food science in Europe” (FUFOSE), re-emphasized the importance in nutritional science of understanding the sequential relationship between initial exposure to dietary component, usually a nutrient, in its dietary matrix, the intestine uptake and transfer of the nutrient and/or its metabolites to the body, the subsequent intermediate metabolism of fate of the component itself, and their ultimate effect on organ or tissue architecture and function including, with particular relevance to health claims to improved physiological, or behavioural function, or a reduced risk of disease [2]. FUFOSE illustrated how this mechanistic schema could be explored to demonstrate evidence of causality based on the use of good quality-assured science and validated markers that demonstrated the strength of causal inference in the individual steps of the chain, and the chain overall.

An important uncertainty in this chain is the efficiency with which the dietary component is utilized systemically, that is, the component’s bioavailability. Evidently, there is a need to relate the systemic outcome to the initial exposure and internal body burden if one is going to use that information to develop reference values, or to develop a case justifying a health claim, or a safe upper limit of intake. Bioavailability is therefore not just an important concept in nutritional science, but also, an important value. However, to say the least, it is difficult to measure, although many approaches have been used in an attempt to do so. Most of these do not measure bioavailability according to the above definition—probably the incorporation of iron into haemoglobin is the best example of the few outcomes that actually measure “bioavailability.” Otherwise, the various and diverse methods which have been used to measure bioavailability measure different variants of true or net intestinal or mucosal uptake and transfer of a nutrient and do not consider the further systemic metabolism, excretion and utilization of the dietary component. Furthermore, what is often measured and called bioavailability focuses on the characteristics of the component and of the dietary matrix as they affect the intestinal uptake and transfer of the component to the neglect of host factors which set the intestinal mucosa for the absorption of the component in question. As such, the term “bioavailability” has more often than not been applied to some aspect of absorption in such a way as to suit the experimental design

rather than to address a pivotal generic phenomenon of nutritional science. This uncritical use of “bioavailability” has no value in objective nutritional risk assessment and cannot be expected to withstand forensic examination. In fact, to accommodate the complete concept of bioavailability, it is arguable that the term has become devalued and an impediment to transparent and objective assessment of dietary nutritional and risk assessment. A potentially more rewarding approach would be to adopt from nutrition’s sister disciplines of pharmacology and toxicology the analysis of systemic metabolism of a component with the Absorption, Distribution, Metabolism, Excretion (ADME) model. This would provide the basic dose–response data relevant to intake and metabolism of a dietary component and its subsequent effects on the host; should the appropriate data not exist, then it would enable a clear exposition of the relevant uncertainties in the nutritional and risk assessment of a dietary component.

The components of an ADME schema fit well with the mechanistic schema envisaged by FUFOSE as a means of addressing the functionality of foods or food components and assessing the evidence available which could be appraised against the FUFOSE construct. “Health claims” relate to what a food or food constituent does in relation to nutritional or physiological beneficial effects such as contributions to health maintenance, health improvements and disease risk reduction. Consumers should be able to make informed choices based on clear and accurate information and to have confidence in the scientific and regulatory processes used to support claims. Many of the recent and ongoing developments on the scientific substantiation of health claims with particular reference to approaches come from activities of Codex, the European food safety authority (EFSA) and the US Food and Drug Administration (US FDA). These authorities have developed and adopted methodologies for the assessment of the totality of the available data and for a suitable framework for weighing the evidence to reflect state-of-the-art nutrition science, to promote future research and to determine the extent to which a causal relationship can be demonstrated. In these approaches, scientific assessments need to be proportionate to meet the legitimate expectations of researchers and applicants for the authorization of a health claim, and there is a need to link the totality of the available data and the strength, consistency and biological plausibility of evidence to claims that are truthful and meaningful to consumers. In the European context, another ILSI-Europe hosted Concerted Action the Process for the Assessment of Scientific Support for Claims on Foods (PASSCLAIM) [3] addressed the strategic presentation and integration of all the evidence relevant to, including that which might limit a claim, supporting causality. It placed no particular emphasis or hierarchical precedence of the

types of evidence used but rather emphasized the expectation that the integrity and coherence of the evidence should be assessed on a case-by-case basis by appropriately competent assessors and that these assessments would be accompanied by an exposition of any uncertainties which might limit confidence in any claimed causal inference.

The expectations and analyses of evidence relevant to claims have become conditioned by the expectations of evidence-based approaches. The underpinning assumption being that evidence-based medicine (EBM) represents the use of current best evidence in making decisions about clinical care and that randomized controlled trials (RCTs), systematic reviews and meta-analyses of such trials are best practice, and there is little need, therefore, to heed other forms of evidence such as cohort studies or expert opinion. Somewhat paradoxically, therefore, clinical recommendations and guidelines are most frequently made by expert committees who themselves evaluate the evidence. Interestingly, evaluation of RCTs versus observational studies shows they produce very similar findings overall [4]. The gold-standard RCT is difficult to apply to nutrition for several reasons. It is practically impossible to create a “study nutrient free” placebo group. While drugs often have a single target, nutrition most often has multiple targets. Effect size for nutrition may be small, but across multiple systems. However, small effects can be very important at the population level. Dose–response relationships between nutrient intake and outcome are often non-linear and may be different for different outcomes. There may be interactions (additive, synergistic, antagonistic) with other nutrients or with drugs. Failure to recognize these features may explain the failure of some nutrition RCTs and wrong conclusions and judgements can be made as a result. Systematic reviews and meta-analyses are increasingly being applied to nutrition and, being based mainly upon RCT evidence, can suffer from the same confounding features. The earliest detailed descriptions of EBM recognized that observational data and expert judgement are essential parts of the EBM decision-making process [5] and appreciated that RCTs were developed to compensate the lack of information and quality assurance about underpinning mechanisms and the difficulty to muster sufficient information to enable an adequate appraisal by the Hill principles [6]. The crucial element in this context is the competency and appropriate knowledge of those who review and assess evidence. It is important that systematic reviews be conducted by persons with expertise in the subject being reviewed. The setting of dietary and nutrient guidelines and recommendations has typically (and rightly) valued expert opinion, and often cohort studies have been considered as providing evidence of at least equal import to that of RCTs. It is clear that, although the philosophy to use the best quality evidence is

shared between “medicine” and “nutrition,” the approach used to evaluating the totality of the relevant evidence needs to be different. As used to support policy and to satisfy regulatory requirements, evidence-based nutrition (EBN) and EBM are different. However, the improving mechanistic insights available through modern cell biology and its integration into systemic physiology has opened up opportunities for the more extensive use of mechanistic and metabolic markers relevant to assessing in an exposure-related fashion the functional and toxic effects of food components; this is congruent with the FUFOSSE mechanistic schema and with a more integrated analysis of the available data as a process of evidence-based mechanistic reasoning [7, 8].

Challenges with vitamin D, fish oils and vitamin E

The workshop considered two situations that exemplify the difficulties of performing nutritional assessment in which assessments would probably benefit from more information of the bases of the available observations. In the first instance, vitamin D is well known for increasing calcium absorption and enhancing bone health. Substantial epidemiological evidence and significant clinical trial data suggest that vitamin D intake can have important effects on the risk of falls, cancer, cardiovascular disease and other health effects. Given the available evidence today summarized in several meta-analyses, vitamin D supplementation for fall prevention should not be delayed as a health claim and general recommendation among the senior population. This suggestion is in line with the Agency for Healthcare Research and Quality (AHRQ) for the US Preventive Services Task Force [9], the 2010 American Geriatric Society/British Geriatric Society Clinical Practice Guideline [10], the 2010 assessment by the IOF [11], the 2011 endocrine society clinical practice guideline [12], and the recent opinion by the EFSA [13], all of which identified vitamin D as an effective intervention to prevent falling in older adults.

In contrast, the Institute of Medicine (IOM) report published in 2010 concluded that the data of vitamin D on fall prevention is inconclusive [14]. However, the evidence for vitamin D's effects on falls has been misinterpreted by the IOM disregarding the overall benefit across all trials in their analyses and most subgroups defined by the IOM.

For other non-skeletal endpoints of vitamin D, there are data from large cohort studies, small clinical trials and mechanistic studies that support a benefit of higher 25-hydroxyvitamin D concentrations on cardiovascular health, immunity and cancer prevention (especially colorectal cancer). However, these health benefits have not been confirmed by large randomized trials, and therefore,

the health claims cannot be substantiated. Notably, however, lack of large randomized trials does not mean lack of benefit as suggested by the IOM report [15].

A similar area of difficulty is the appraisal of the impact of fish oils and vitamin E on human health. Large observational studies, randomized clinical trials and experimental studies have evaluated the effects of fish eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) consumption on fatal coronary heart disease and sudden cardiac death. These studies provide concordant evidence that modest consumption of fish or fish oil (1–2 servings/week of oily fish or ~250 mg/day of EPA and DHA) substantially reduces the risk of coronary heart disease and sudden cardiac death. Pooled analysis of randomized clinical trials and prospective cohort studies demonstrates a 36% lower risk of coronary heart disease and 17% lower risk of total mortality comparing 0 and 250 mg/day of EPA and DHA with little additional benefits with higher intakes. Observational studies utilizing tissue biomarkers of n-3 fatty acids, the reductions in risk are even larger. Intake of 250 mg/day of EPA and DHA appears sufficient for primary prevention. A variety of seafood should be consumed; individuals with very high consumption (≥ 5 servings/week) and pregnant and nursing mothers should consume 2 seafood servings/week, limiting the intake of species highest in mercury levels. On the basis of both the strength of the evidence and the potential magnitude of effect, the benefits of fish intake exceed the potential risks. Moderate consumption of fish and fish oil should be among the first-choice preventatives for coronary heart disease and sudden cardiac death.

Although the hypothesis that vitamin E may reduce the risk of cardiovascular disease and cancer is an intriguing area of research, it continues to be an unproven hypothesis. Inconsistent findings, and some data that indicate the potential for adverse effects from very high intakes of vitamin E, suggest that we exercise caution against making premature recommendations for high intakes of vitamin E. Recommendations from research need to be addressed and verified in multiple studies using a variety of designs. Thus, the use of health claims on foods presents a problem: conveying a message in a compact way to be readily grasped by the lay person and passing a reality check on a topic not fully supported by available scientific evidence. The problem results, of course, from the very definition of health, which encompasses acute and chronic, young and old, prevention and treatment. Disease risk is generally being looked at on a population basis, not on an individual basis, and this will probably remain so before significant advances in personalized medicine will have occurred. In addition to the recognized nutrients, research interests have focused on protection by flavanol-rich foods against vascular dysfunction and oxidative damage. The recent EFSA

analyses on foods and micronutrients illustrate that the type and level of scientific evidence required to substantiate health claims continue to be an issue. Further to this issue, however, will be the challenges of justifying multiple benefits from single dietary components or groups of components or of single benefits derived from multiple dietary components. Both these scenarios are important in the context of health but as yet the justification of these as with water-soluble tomato components [16].

Nutraceuticals, supplements and claims

Dietary supplements (term used by US FDA), food supplements (term used in Europe) or nutraceuticals (terminology of Health Canada) show specific nutritional value and/or provide specific healthy or body function effects. The characteristic values of such food products are defined and promoted by food or health claims. Due to their origin and long-term use, nutraceuticals are considered safe. Their claims have to be justified by portions ingested in the product and scientifically proven in a target population. The claim must be understandable by the consumers. Such products, especially when defined by health claims, are positioned between ordinary food and drugs (medicinal products); they are intended to strengthen or protect the healthy state. The market for these products is attractive and rapidly growing. National regulations are often not consistent, thereby hindering internationally harmonized market access on levels of notification or specific regulations.

EFSA evaluates and harmonizes the health claims from the European Union (EU) Member States as a scientific adviser to the European Commission (EC). These statements are used for approval and market access according to the defined categories of products and claims, which finally also determine the product declaration.

Supplements have some peculiarities that influence the scientific approach and proof of efficacy. Neglecting such aspects may result in conflicting study results and, therefore, require careful consideration for evaluation and use [17, 18]. EFSA has done a large volume of work to harmonize and consolidate requested 44,000 claims to actually about 2,800 (80% denied). Most are classified in generally accepted functional claims (article 13.1) and nutrition claims according to a positive list. Few innovative claims (article 13.5) or risk reduction and children's health claims (article 14) have been approved because of the heavy burden for scientific proof and a clear product–effect relationship (causality), although some have been approved [13].

Even so, the EFSA NDA panel's decisions are often considered difficult to understand and to interpret.

Furthermore, there are concerns about the transparency and consistency of the evaluation procedures: The absence of a clear template for evaluations and reports increases these concerns.

If the scientific assessment statements of EFSA do not provide an appropriate and transparent assessment of causal inference, then legal disputes are inevitable [19]. There is a clear need to improve the guidance and exchange with all relevant stakeholders to sustain and develop the potential of safe and effective supplements to play a cost-efficient role for health maintenance in consumers at risk [20].

Nutrient reference values and public understanding of nutrition

Nutrient reference values are expected to inform and educate consumers, and their content and effectiveness in achieving this were reviewed. Codex established the *Guidelines on Nutrition Labelling* in 1985, indicating that numerical information on vitamins and minerals should be expressed in metric unit and/or as a percentage of the nutrient reference values (NRVs). The *Codex Guidelines for Vitamin and Mineral Food Supplements* (CAC/GL 55-2005) [21] and *Codex Guidelines for Use of Nutrition and Health Claims* (CAC/GL 23-1997, Rev. 1-2004) [22] also indicate the NRVs as a basis for expressing nutrient content and for criteria of nutrition and health claims in food labelling. Following the recommendations of 1988 Helsinki Expert Consultation, a single set of NRVs currently in use was set in 1993 for nine vitamins (A, D, C, thiamine, riboflavin, niacin, B₆, folic acid/folate and B₁₂) and five minerals (Ca, Mg, Fe, Zn and I). In 2004, the Codex Committee on Nutrition and Foods for Special Dietary Uses (CCNFSDU) agreed to add and update the current Codex NRVs for vitamins and minerals. This is particularly important because reference nutrient intake values have been expanded into multiple categories since the mid-1990s, most notably the average requirement (AR) and individual nutrient level, at 98th percentile (INL₉₈). Therefore, the major concerns in this revision were to determine which category of these reference nutrient intake values should be used as the basis for nutrition labelling and which age groups should be considered for use consistently throughout the labelling process to provide consumers with simple, coherent, understandable and meaningful reference points. The CCNFSDU has developed principles for the first stage of the process. The INL₉₈ was considered to be the preferable measure because, by definition, it meets the requirements of practically all who will be using the label in the population. Regarding age groups, CCNFSDU considered that a weighted approach

based on the relative proportions of the different age groups above 36 months throughout the life cycle would be impractical at the international level. As the major proportion of the population in most countries is adults, the CCNFSU selected a simple arithmetic mean of adult males and females in the age range 19–65 years for males and 19–50 years for premenopausal females excluding pregnancy and lactation, consistent with the age ranges published by World Health Organization/Food and Agriculture Organization (WHO/FAO). One of the most difficult challenges for the manufacturer and the regulator is to anticipate how the NRVs and other information on labels will be understood and utilized by the consumer. Consequently, in the absence of data from appropriately designed studies, there is much disagreement about how the consumer will use the information on the label. Further, in this vacuum, regulatory and policy authorities around the world have taken many different approaches to the development of related policy. A worthwhile goal for industry and regulatory authorities should be the reduction of reducing the label information asymmetry from one country to another—especially in Europe under the EU and among all countries in order to facilitate trade. Despite an abundance of research in this area, no consensus as to the optimal labelling system has yet developed.

A global legislative perspective: WTO and Codex Alimentarius

In maintaining and developing its market, the food supplement industry, assuming the cooperation of a sponsoring government, can use the WTO international trade rules as part of advocacy efforts or in formal dispute settlement to address regulatory hurdles affecting their business. Legal arguments against two particular regulatory initiatives have been developed and are available.

First, regulatory measures which restrict the sale of vitamin and mineral food supplements by establishing maximum levels of nutrient content based solely on recommended dietary allowances (RDA) appear to violate WTO rules, because they (1) are not based on a risk assessment nor sufficient scientific evidence, (2) are more burdensome than standards applicable to producers of comparable products such as certain conventional foods, and (3) exceed the level of protection of a relevant international (Codex) standard without scientific justification. In addition, it can be argued that such regulatory restrictions are more trade-restrictive than necessary and have the effect of creating unnecessary obstacles to international trade, because less trade-restrictive alternatives (e.g. labelling with maximum intake information combined with higher maximum nutrient levels based on a risk assessment) are available.

Second, EFSA and the European Commission's application of the EU Nutrition and Health Claims Regulation may be overly restrictive in violation of WTO rules. If the European Commission acts upon the EFSA's negative opinions on almost all health claims relating to food supplements not containing vitamins or minerals, it can be argued that the regulation and its conformity assessment procedures as applied are more trade-restrictive than necessary and result in an unnecessary obstacle to international trade, in particular because the EFSA (1) consistently failed to take into account and weigh the totality of the available evidence, (2) applied drug-like standards to claims for food products, and (3) did not apply different standards to different claims, but instead subjected all claims to the highest standard. The trade-restrictive impact of the EFSA's approach will be severe if the EC acts upon its opinions, while a less trade-restrictive approach (e.g. weighing all the evidence and taking into account the end-use and nature of the claims and products) would not lead to significant risks for consumers.

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